

# Pathophysiology of anorexia in the cancer cachexia syndrome

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## Abstract

Anorexia is commonly present in persons with cancer and a major component of cancer cachexia. There are multiple causes of anorexia in cancer. Peripherally, these can be due to (i) substances released from or by the tumour, e.g. pro-inflammatory cytokines, lactate, and parathormone-related peptide; (ii) tumours causing dysphagia or altering gut function; (iii) tumours altering nutrients, e.g. zinc deficiency; (iv) tumours causing hypoxia; (v) increased peripheral tryptophan leading to increased central serotonin; or (vi) alterations of release of peripheral hormones that alter feeding, e.g. peptide tyrosine tyrosine and ghrelin. Central effects include depression and pain, decreasing the desire to eat. Within the central nervous system, tumours create multiple alterations in neurotransmitters, neuropeptides, and prostaglandins that modulate feeding. Many of these neurotransmitters appear to produce their anorectic effects through the adenosine monophosphate kinase/methylmalonyl coenzyme A/fatty acid system in the hypothalamus. Dynamin is a guanosine triphosphatase that is responsible for internalization of melanocortin 4 receptors and prostaglandin receptors. Dynamin is up-regulated in a mouse model of cancer anorexia. A number of drugs, e.g. megestrol acetate, cannabinoids, and ghrelin agonists, have been shown to have some ability to be orexigenic in cancer patients.

**Keywords** Anorexia; Cancer cachexia syndrome; Pathophysiology; Loss of appetite

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## Introduction

Anorexia (loss of appetite) is a common concomitant of cancer.<sup>1</sup> Anorexia in cancer has many causes, but the primary cause is often an increase in pro-inflammatory cytokines or an increase in lactate. These two factors then modulate central nervous system neurotransmitter cascades. In this article, we will review the pathophysiology of cancer anorexia and its treatment. For this literature review, we ran a PubMed search based on the keywords ‘anorexia cachexia cancer’, and we generated 1170 results. We reviewed 650 abstracts, of which we read 233 articles. Abstracts that were not read were because the title made it obvious that it was a review or not relevant to this review. In addition, we also utilized references in some of these articles and the awareness of one of us (J. E. M.) of other pertinent articles. The decision on whether or not an agent was a mediator was based on the senior author’s

opinion. In most cases, there is inadequate experimental data to determine the importance of any single mediator. This is a narrative review. It is important to recognize that the anorexia associated with cancer is derived from conserved evolutionary responses to the physiological challenges of cancer. In addition, there is a secondary set of responses due to the variety of toxins that are currently infused into patients in an effort to cure the primary disease. It is the overlap of these two responses that leads to the cancer cachexia syndrome.

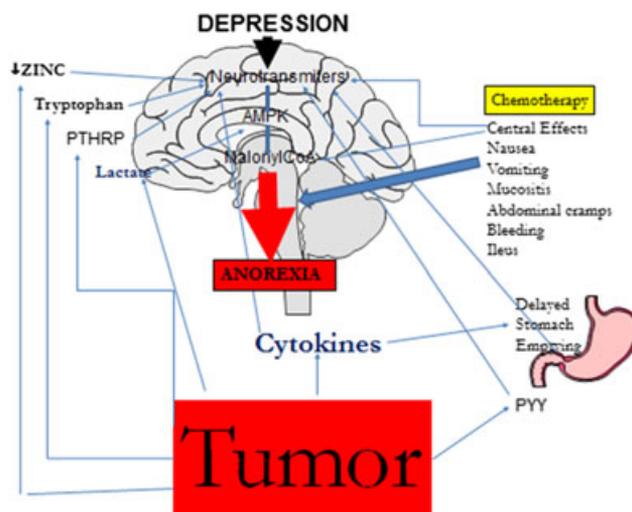
## Causes of anorexia

There are numerous causes of anorexia in cachexia (*Figure 1*).<sup>2</sup> These can be conveniently categorized as being due to central or peripheral mechanisms. In each group, there are also a series of secondary causes due to chemotherapy.

**Figure 1** Causes of anorexia in cachexia.

PTH-RP = parathyroid-related peptide;

PYY – peptide YY; AMPK = AMP kinase



Peripheral causes can be directly due to (i) tumours causing dysphagia or directly impinging on gastrointestinal function; (ii) tumours producing substances that alter food intake, e.g. lactate, tryptophan, or parathormone-related peptide<sup>3</sup>; (iii) tumours leading to alterations in nutrients resulting in anorexia, e.g. zinc; or (iv) tumours producing inflammation leading to cytokine release. Alterations in gastrointestinal function can alter visceral receptor function, leading to altered secretion of gastrointestinal peptides, e.g. peptide tyrosine tyrosine (PYY), and alterations in stomach emptying can alter feedback of satiating hormones.<sup>4</sup> Peripherally, chemotherapy can alter taste perception and cause nausea, vomiting, mucositis, abdominal cramping, bleeding, and ileus. Dysgeusia is present in 39% of patients receiving chemotherapy.<sup>5</sup>

Central causes of anorexia can be depression, pain, or a variety of alterations in central neurotransmitters. The neurotransmitter changes in depression that lead to anorexia appear to be alterations in serotonin and corticotrophin-releasing factor (CRF).<sup>6,7</sup> When cancer patients are infused with interferon, there is an increased kynurenic/keurinic acid, which is associated with depression and anorexia.<sup>8</sup> This leads to alterations in tryptophan and serotonin levels. Sickness behaviour is due to a variety of pro-inflammatory cytokines. The behavioural characteristics of sickness behaviour consist of fatigue, weakness, social withdrawal, sleepiness, sadness, lack of motivation, hyperalgesia, failure to concentrate, and anorexia.<sup>9</sup> Hypoxia has been considered to lead to anorexia in patients with head and neck cancer.<sup>10</sup>

There is some evidence that some of the central anorectic effects of chemotherapy involve ghrelin (*vide infra*). Methotrexate leads to a decrease in proopiomelanocortin (POMC) messenger RNA (mRNA) (potentially decreasing opioid-mediated feeding) and activation of brain pathways associated with dehydration.<sup>11</sup> Tamoxifen, which induces anorexia when used for the treatment of breast cancer, inhibits fatty acid synthase in the hypothalamus, leading to an accumulation of malonyl coenzyme A (CoA).<sup>12</sup> Increased malonyl CoA is associated with anorexia in cancer (*vide infra*). Common chemotherapeutic agents act on the chemo-receptor trigger zone, which contains serotonin 5-HT<sub>3</sub> receptors. These receptors activate neurokinin-1 receptors, leading to emesis.<sup>13</sup> At present, there is limited information on how chemotherapeutic agents produce anorexia in cancer patients.

## Cytokines and adipokines

Cytokines are a group of peptide hormones that are released from the immune system or from tumours themselves.<sup>14</sup> They can act in either a paracrine, autocrine, or endocrine fashion. Cytokines generally act in a synergistic or antagonist cascade system to produce their effects. Inflammatory cytokines such as tumour necrosis factor alpha (TNF $\alpha$ ), interleukin-1 (IL-1), and interleukin-6 (IL-6) are elevated in many cancers.<sup>15,16</sup> Administration of cytokines to rodents has been demonstrated to reduce food intake.<sup>17–19</sup>

Interleukin-1, which is produced by lymphocytes and macrophages, is the most potent anorectic cytokine. IL-1 reduces the size, duration, and frequency of meals but does not reduce the desire for food.<sup>20</sup> IL-1 has its most potent anorectic effects when injected into the ventromedial hypothalamus.<sup>21</sup> It can produce its effects either by directly crossing the blood–brain barrier or by activating ascending fibres of the vagal nerve to release IL-1 in the central nervous system.<sup>22</sup> Antibodies to IL-1 enhance food intake in tumour-bearing rodents.<sup>23</sup> IL-1 enhances serotonin activation, leading to increased POMC activity.<sup>24</sup> IL-1 stimulates CRF production in the hypothalamus, leading to anorexia.<sup>25</sup> The anorectic effect of IL-1 can be partially blocked by antibodies to CRF.<sup>25</sup> IL-1 alpha is the major peripheral mediator, whereas within the brain, it is the paracrine effects of IL-beta that are more important.

Interleukin-6 is secreted by T-cells and macrophages as well as microglia, astrocytes, and neurons. While there is evidence that IL-6 plays a role in the cachexia of colon adenocarcinoma-26 bearing mice, these tumours do not produce anorexia in the host, suggesting that IL-6 does not play a role in cancer anorexia.<sup>26</sup>

Monocytes, macrophages, and tumours produce TNF $\alpha$ . TNF $\alpha$  levels are increased in cachectic mice.<sup>27</sup> TNF $\alpha$  produces anorexia either peripherally or centrally.<sup>28</sup> It can cross the

blood–brain barrier<sup>29</sup> or produce its effects by stimulating ascending fibres of the vagus.<sup>30</sup> An inhibitor of TNF $\alpha$  increased food intake in anorectic tumour-bearing rats.<sup>28</sup> The TNF $\alpha$  rs800629 single-nucleotide polymorphism is associated with anorexia in patients with non-small-cell lung cancer.<sup>31</sup>

Interferon- $\gamma$  reduces meal size when administered into the cerebral ventricles.<sup>32</sup> Anti-interferon- $\gamma$  antibodies reverse cachexia in mice with Lewis lung tumours.<sup>33</sup> Cytokines stimulate immunoreactive nitric oxide synthase in the hypothalamus, suggesting a mechanism by which they alter central neuropeptides.<sup>34</sup> Figure 2 provides an overview of the potential mechanisms by which cytokines may produce anorexia.

Leptin is an adipokine, produced from fat cells, that produces anorexia within the central nervous system.<sup>35</sup> There is no evidence that leptin plays a role in cancer anorexia.<sup>24</sup> There is also no evidence for a role in the pathogenesis of cancer anorexia for adiponectin, resistin, and chimerin.

Visfatin or pre-B colony-enhancing factor (PEBF) or nicotinamide phosphoribosyl transferase (Namprt) is a cytokine that

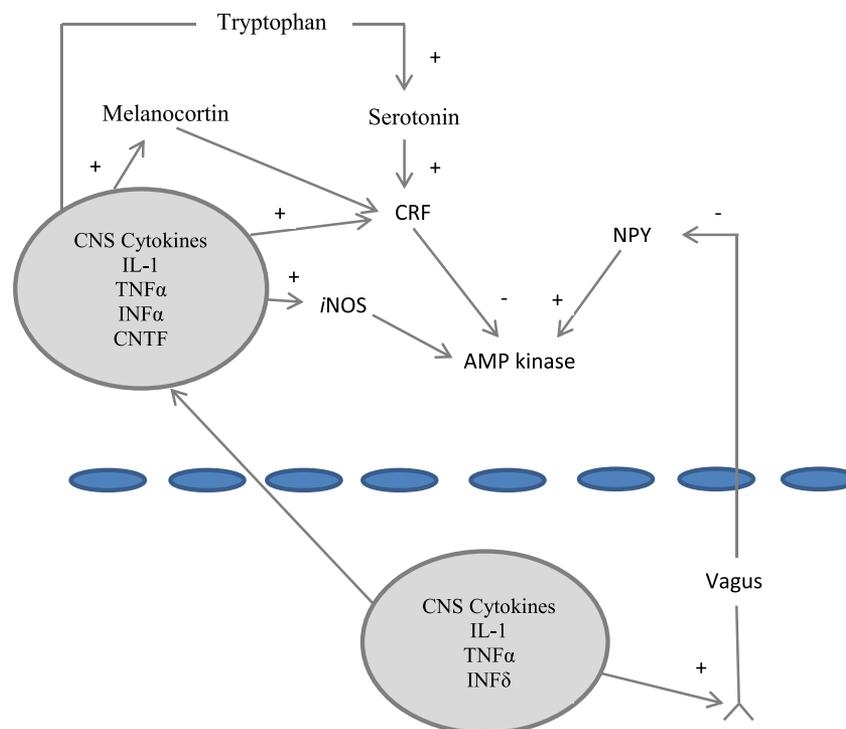
is involved in obesity by promoting vascular smooth cell maturation and inhibition of neutrophil apoptosis in the presence of IL-7 and stem cell factors. Its gene, PEBF, is encoded as a pseudogene in chromosome 10.<sup>36</sup> Its role is in catalysing the conversion of nicotamide with 5-phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide. Nicotinamide mononucleotide is an adipokine substrate that promotes insulin sensitivity by mimicking insulin and lowering blood sugar levels. Its serum level is increased in obese patients because of its expressivity in visceral tissues. Cell culture experiments and high visfatin levels in mice after a high-fat diet have shown that visfatin contributes to metabolic syndrome in obese patients.<sup>37</sup> Visfatin elevation in obese patients was described by Haider *et al.*<sup>37</sup> After 6 months, gastric banding decreased visfatin level and leptin but increased adiponectin level.

Cancer cells have increased levels of visfatin, and Namprt/PEBF/visfatin plays a role in cancer signalling pathways. It was first discovered in increased levels in colorectal cancer.<sup>38</sup> Moreover, cells that overexpressed Namprt/PEBF/visfatin were more resistant to chemotherapy than cell lines

**Figure 2** Potential mechanisms by which cytokines produce anorexia.

IL-1 = interleukin 1; TNF $\alpha$  = tumor necrosis factor alpha; INF $\gamma$  = interferon  $\gamma$ ; CNTF = ciliary neurotrophic factor; *i*NOS = inducible nitric oxide synthase; NPY = neuropeptide Y;

CRF = corticotrophin



with stable knockdown of *Namprt/PEBF/visfatin* genes.<sup>39</sup> In addition, prostate cancer cells with exogenous expression of visfatin genes show rapid tumour cell proliferation.<sup>40</sup>

Intracerebroventricular administration of visfatin decreased food intake, resulting in weight loss.<sup>41</sup> This was associated with an increase in POMC mRNA and  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH). The decrease in food intake was prevented by the administration of SHU9119, an inhibitor of melanocortin receptor 3 and melanocortin receptor 4 (MC4R). While the visfatin data are somewhat paradoxical, it can be hypothesized that this is due to an attempt of the body to protect itself against the anorectic effect of visfatin.

## Lactate

Malignant tumours often have an increase in glycolysis associated with an increase in lactic dehydrogenase activity (LDH).<sup>42</sup> The LDH is of the type that preferentially converts pyruvate to lactate.<sup>43</sup> Numerous studies have found an increase in LDH and lactate in the serum in both experimental tumour-bearing animals<sup>44–46</sup> and humans with cancer.<sup>47–51</sup>

A number of studies have found that lactate is a potent anorectic agent. Bales *et al.*<sup>52,53</sup> reported that lactate reduced feed intake in goats and monkeys. Spontaneous food intake is inhibited after both intravenous and intraportal infusion of lactate in rats.<sup>54</sup> Lactate infusion into the carotid artery of rats decreased levels of c-Fos in the paraventricular nuclei of the hypothalamus.<sup>55</sup> This effect of lactate activates glucose responsive neurons in the ventromedial hypothalamus, resulting in a reduction in satiation. Lactate infusion into the hypothalamus plays a key role in glucosensing and regulation of food intake.<sup>56–59</sup> Lactate can be transported across the blood–brain barrier by monocarboxylate transporters.<sup>60</sup> Thus,

a peripheral increase in lactate can interfere with the glucosensing mechanisms in the hypothalamus, which is dependent on the interaction of tanycytes and neuronal cells secondary to lactate flux through monocarboxylate transporters. Physiologically, this system regulates food intake via orexigenic neurons [synthesizers of neuropeptide Y (NPY) and agouti gene-related peptide (AGRP)] and anorectic POMC neurons by altering the activity of the monocarboxylate transporter 4. Lactate infusion decreased food intake in humans.<sup>61</sup> In persons undergoing peritoneal dialysis, lactate-based dialysis solutions are more anorectic than are bicarbonate-based solutions.<sup>62,63</sup>

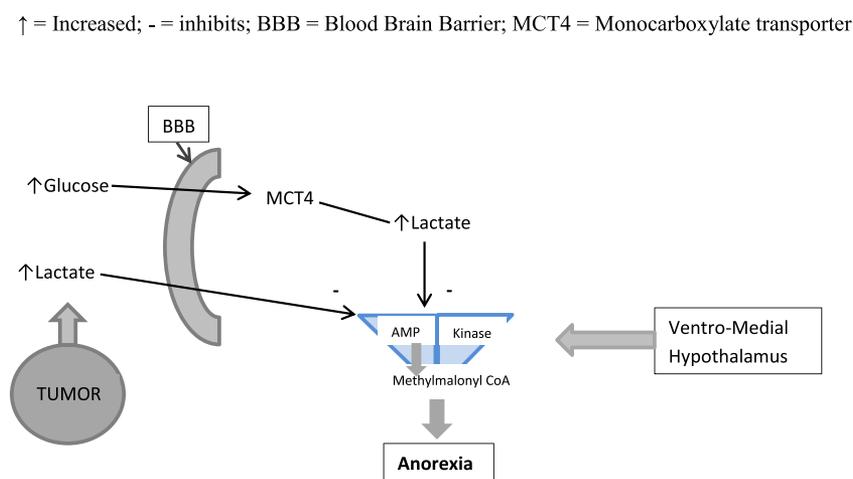
Lactate levels increase in tumour-bearing animals but not in pair-fed animals.<sup>64</sup> In tumour-bearing animals, lactate levels increased contiguously with the onset of anorexia.<sup>65</sup> Lactate infusion was associated with elevated levels of NPY in the ventromedial hypothalamus and dorsomedial hypothalamus, but there was no alteration in CRF. Lactate suppresses food intake by activating adenosine monophosphate (AMP) kinase/methylmalonyl CoA signalling pathway<sup>66</sup> (Figure 3). Dichloroacetate enhances pyruvate dehydrogenase, leading to a reduction of lactate. Dichloroacetate failed to decrease anorexia in tumour-bearing rats.<sup>65</sup> This may be due to conflicting effects of dichloroacetate on central levels of lactate.

Overall, it would appear that lactate is a strong candidate for one of the reasons why cancer is associated with anorexia.

## Monoamines

Historically, studies have shown that norepinephrine is a potent enhancer of food and serotonin is an anorectic agent.<sup>67</sup> Dopamine appears physiologically to increase motivation for food intake.<sup>68</sup>

**Figure 3** Lactate mechanism of tumour induced anorexia.



In 1979, Krause *et al.*<sup>69</sup> found that anorectic rats carrying a Walker 256 tumour had increased plasma free tryptophan, brain tryptophan, and 5-hydroxyindole acetic acid. These results suggested a role of serotonin in cancer anorexia. In 1986, Rossi Fanelli and his colleagues<sup>70</sup> found that plasma free tryptophan was elevated in cancer patients with anorexia. In addition, the free tryptophan-to-neutral amino acid ratio was elevated in cancer patients with anorexia and early satiety compared with controls and with non-anorectic cancer patients. Another study reported that plasma and cerebrospinal fluid tryptophan were increased in persons with cancer anorexia.<sup>71</sup> Surgical ablation of tumours in cancer patients reduced plasma tryptophan and anorexia.<sup>72</sup> Utilizing a branched-chain amino acid supplement designed to reduce tryptophan entry into the brain and thus serotonin synthesis improved appetite in cancer patients.<sup>73</sup>

In other tumour models in rats (MCG101), serum tryptophan does not correlate with food intake,<sup>74</sup> and in cancer anorectic humans given interleukin 2, plasma tryptophan levels are low.<sup>75</sup> Overall, these data suggest that tryptophan elevations may play a role in some, but not all, anorexia associated with cancer.

Chance *et al.*<sup>76</sup> found elevated tryptophan, serotonin, and 5-hydroxyindole acetic acid in a variety of brain areas in rats with Walker 256 tumours. They found similar increases in the brains of the methylcholanthrene-induced sarcoma model of cancer anorexia. However, serotonin depletion in rats with the Walker 256 tumour had minimal effects on food intake.<sup>77,78</sup> Similarly, the serotonin antagonist failed to increase feeding after injection into the ventromedial nucleus of the hypothalamus in tumour-bearing rats.<sup>79,80</sup> Other studies have also shown an activation of serotonin in the hypothalamus in methylcholanthrene sarcoma rats, which could be reversed by surgical removal of the tumour.<sup>81</sup> Using *in vivo*/microdialysis tumour-bearing rats increased the serotonin-to-dopamine ratio.<sup>82</sup> In tumour-bearing rats, the hypothalamic serotonin (5-HT<sub>1B</sub>) receptor is up-regulated, and tumour resection leads to normalization of food intake and the serotonin receptor.<sup>83,84</sup> Serotonin levels increase and dopamine levels decrease in the hypothalamus of rats with cancer anorexia.<sup>85</sup>

Finally, in humans with cancer, small increases of food intake have been seen with the serotonin antagonist cyproheptadine, the serotonergic-3-receptor blocker, ondansetron, ramosetron, and granisetron.<sup>75,86,87</sup> However, this small increase did not alter the cachexia-associated weight loss.

In general, dopamine levels appear to be decreased in hypothalamic nuclei of tumour-bearing animals.<sup>85,88,89</sup> Dopamine receptors (D1 and D2) are increased in tumour-bearing animals.<sup>90</sup> The D2 dopamine antagonist, sulpiride, increased food intake in tumour-bearing rats when injected bilaterally into the supraoptic nucleus.<sup>19</sup> This effect is due to an increase in meal size.<sup>90</sup>

There is a paucity of data on norepinephrine effects on cancer anorexia. In the Walker 256 cancer model, there was an increase in hypothalamic norepinephrine at night, which correlated with the size of the rats' food intake.<sup>91</sup> In a benzo(a)pyrene murine fibrosarcoma, norepinephrine levels were reduced.<sup>92</sup> In a murine lymphoma cell line, norepinephrine levels were increased.<sup>93</sup> Norepinephrine injections into the hypothalamus continued to elicit feeding during the anorexic phase in methylcholanthrene sarcoma-bearing rats.<sup>94</sup> These data suggest that the norepinephrinergic system increases its activity in some cancers in an attempt to overcome cancer cachexia.

## Peptides, nitric oxide, and adenosine monophosphate kinase

A number of gastrointestinal peptides such as cholecystokinin (CCK), bombesin-like peptides, amylin, and glucagon-like peptide-1 have been demonstrated to be anorectic in animals and humans.<sup>95–100</sup> There are little data on changes in these peptides and their relationship to anorexia in cancer in either animals or humans. CCK is unaltered peripherally in tumour-bearing rats but may be increased in the central nervous system.<sup>101</sup> CCK8 levels were not elevated in anorectic cancer patients and did not correlate with anorexia severity.<sup>102</sup> An animal study suggested that increases in bombesin-like peptide in salivary glands may play a role in irradiation-induced anorexia.<sup>103</sup> PYY causes severe weight loss when administered peripherally.<sup>104</sup> PYY levels were found to be elevated in children with acute lymphoblastic leukaemia,<sup>105</sup> but not in adults with cancer cachexia.<sup>106</sup> Overall, these studies provide little evidence for peripheral peptides playing a role in cancer anorexia.

In the central nervous system, a number of neuropeptides interact with classical neurotransmitters to regulate food intake.<sup>67</sup> Of these, NPY has been considered one of the most potent orexigenic agents.<sup>107</sup> In rats with the Yoshida sarcoma, NPY concentrations were increased in the arcuate nucleus but decreased in the paraventricular nucleus.<sup>108</sup> CRF, an anorectic peptide, was reduced in both nuclei. This was confirmed by other studies<sup>109</sup> despite an increase in NPY mRNA.<sup>110–113</sup> NPY immunostaining was decreased in the supraoptic nucleus, the parvocellular portion of the paraventricular nucleus, and the suprachiasmatic and arcuate nuclei of tumour-bearing rats.<sup>114</sup> In addition, hypothalamic concentrations of NPY release measured by microdialysis were reduced.<sup>115</sup> Hypothalamic injections of NPY into the hypothalamus of tumour-bearing rats were limited in their ability to increase food intake.<sup>116</sup> The Y1 receptor showed a reduction in the arcuate and paraventricular nucleus of tumour-bearing rats.<sup>117</sup> These studies suggest that, in tumour-bearing rats, there is dysfunction of the NPY feeding

regulatory system. It is possible that this down-regulation of the NPY system is due to overactivation of the POMC/cocaine and amphetamine-regulated transcript system.<sup>118</sup>

There is now evidence that most of the central effect of neuropeptides on feeding is mediated through neuronal nitric oxide synthase (*n*NOS).<sup>119</sup> Nitric oxide antagonists block the effects of NPY, ghrelin, and orexin.<sup>120,121</sup> *n*NOS-knockout mice also block the effects of orexigenic agents.<sup>122</sup> Leptin's anorexic effects are also mediated through *n*NOS.<sup>123</sup> In tumour-bearing mice, *n*NOS was significantly increased in the paraventricular and ventromedial hypothalamus.<sup>124</sup> This suggests that *n*NOS may be increased to try and overcome a distal effect of tumours on anorexia (Figure 4).

Adenosine monophosphate-activated protein kinase has been shown to regulate appetite and to control energy metabolism.<sup>125</sup> Nitric oxide stimulates AMP kinase.<sup>126</sup> Phosphorylated AMP kinase activates acetyl CoA carboxylase, which inhibits the conversion of acetyl CoA to malonyl CoA.<sup>126</sup> Inhibition of malonyl CoA reverses its anorectic effect. In anorectic tumour-bearing rats, infusion of 5-amino-4-imidazolecarboxamide-riboside into the third cerebral ventricle activates AMP kinase.<sup>127</sup> This leads to an increase in food intake in these tumour-bearing rats.

## Melanocortin

Pre-POMC is a 285-amino-acid precursor to its anorexigenic product, POMC, a 241-amino-acid precursor by the translational removal of 44 amino acids.<sup>128</sup> POMC is synthesized in the corticotrophin cells of the anterior pituitary, melanotrope cells of the pituitary, skin melanocytes, nucleus tractus solitarius of the brainstem, and the arcuate nucleus of the hypothalamus. It can be cleaved to form [Met]enkephalin,  $\beta$ -lipotropin,  $\gamma$ -melanotropin ( $\gamma$ -MSH), corticotropin-like intermediate peptide, corticotropin (adrenocorticotrophic hormone),  $\alpha$ -MSH,  $\gamma$ -lipotropin,  $\beta$ -melanotropin ( $\beta$ -MSH),  $\beta$ -endorphin, and N-terminal peptide of POMC. It plays a role in appetite regulation.<sup>129</sup> In the arcuate nucleus, neurons of the cocaine and amphetamine-regulated transcript and POMC are produced by satiety neurons.<sup>130</sup>

In 1989, Tsujii *et al.*<sup>130</sup> found that acetylated  $\alpha$ -MSH decreased food intake after central administration. This effect is secondary to melanocortin receptors 3 and MC4R. AGRP is produced by NPY-expressing cells and is an inverse agonist of the MC4R and blocks the effects of  $\alpha$ -MSH. Our unpublished studies suggest that  $\alpha$ -MSH works through *n*NOS activation (Morley and Farr, unpublished data). POMC neurons have a receptor for IL-1 $\beta$ , which when activated increased  $\alpha$ -MSH release.<sup>131</sup> Leukaemia inhibitory factor is induced by a number of tumours and activates the POMC neurons in the arcuate nucleus, causing the release of  $\alpha$ -MSH.<sup>132</sup> A

number of small-molecule inhibitors of the MC4R are available.<sup>133</sup> Lipopolysaccharide-induced anorexia is reversed by AGRP administered centrally and is resisted in MC4R-knockout mice.<sup>134</sup> AGRP has also been shown to prevent a decrease in food intake in sarcoma-bearing mice.<sup>134</sup> Food intake was preserved in Lewis lung adenocarcinoma-implanted MC4R-knockout mice.<sup>135</sup> A number of other studies in the Lewis lung carcinoma mouse model of cachexia have shown that melanocortin antagonists increase food intake.<sup>136,129,137,138</sup> Melanocortin antagonists also increase food intake in mice implanted with C26 adenocarcinoma cells<sup>139,140</sup> and prostate cancer.<sup>135</sup> However, in a methylcholanthrene-induced sarcoma in rats, an MC4R antagonist failed to reverse the anorexia.<sup>141</sup> In another tumour model, Buffalo rats implanted with Morris hepatoma 7777 cells, the tumour-bearing rats failed to show an increase in AGRP in the hypothalamus, normally seen in food-restricted rats.<sup>142</sup> LC-6 lung cancer-bearing rats secrete parathyroid hormone-related peptide (PTHrP). In these animals, there is a decrease in mRNA and peptide levels of the anorectic agents, POMC, and cocaine and amphetamine-regulated transcript and an increase in NPY and AGRP levels and their mRNA.<sup>143,144</sup> These findings suggest that, in this model of cancer anorexia, POMC works through a mechanism separate from the classic neuropeptide model. It was also shown that this effect was not due to the hypercalcaemia produced by the PTHrP. The C26 colon adenocarcinoma mouse model has increased food intake with increasing food burden and decreased levels of POMC.<sup>145</sup>

Overall, the findings suggest that the melanocortin plays a role in the anorexia produced by some cancers, but in others, the anorectic effect occurs distal to the neurons activated by  $\alpha$ -MSH (Figure 5).

## Dynamin

Dynamin is a 96 kDa guanosine triphosphatase that plays a role in endocytosis in cells. Using proteomic profiling in a mouse model of cancer anorexia, dynamin-1 was up-regulated compared with both tumour-bearing and pair-fed mice.<sup>146</sup> Dynamin-1 is important for the internalization of MC4Rs. In HEK293 cells, dominant negative mutants of dynamin-1 prevent internalization of the MC4R when it is stimulated by  $\alpha$ -MSH.<sup>147</sup> Stimulation of MCR4 leads to anorexia.<sup>134</sup> This suggests that dynamin internalization of MC4Rs is a cellular component of cancer anorexia, possibly acting as a physiological factor to try and attenuate cancer anorexia.

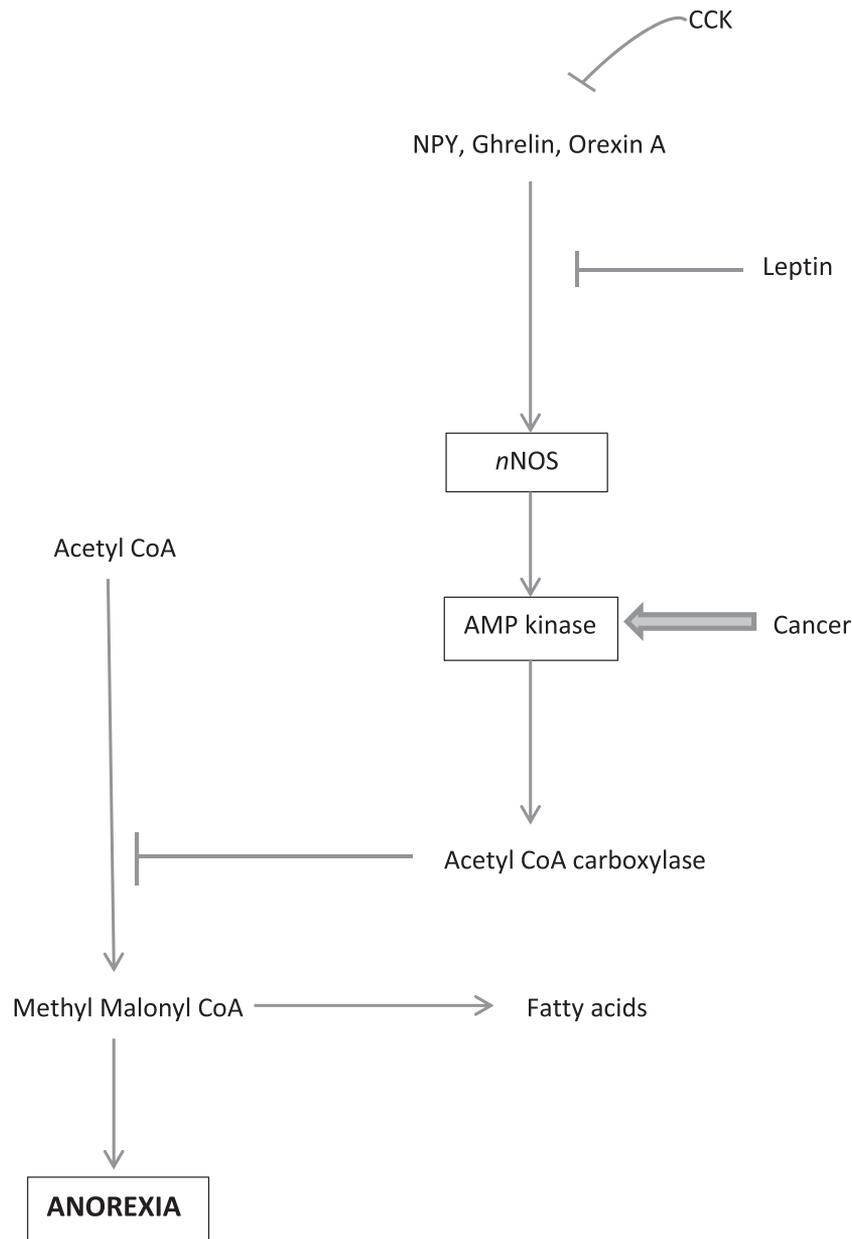
Prostaglandins (PGE2 and PGF2 $\alpha$ ) reduce food intake after central administration.<sup>148</sup> Cyclooxygenase-1 inhibition reduces cancer-induced anorexia.<sup>149</sup> PGE2 activation of the EP4 signalling in the hypothalamus is the mediator of PGE2

**Figure 4** Peptide hormones, nNOS AMP kinase, and cancer anorexia.

AMP kinase and cancer anorexia

NPY = neuropeptide Y, CCK = cholecystokinin

nNOS = neuronal nitric oxide synthase



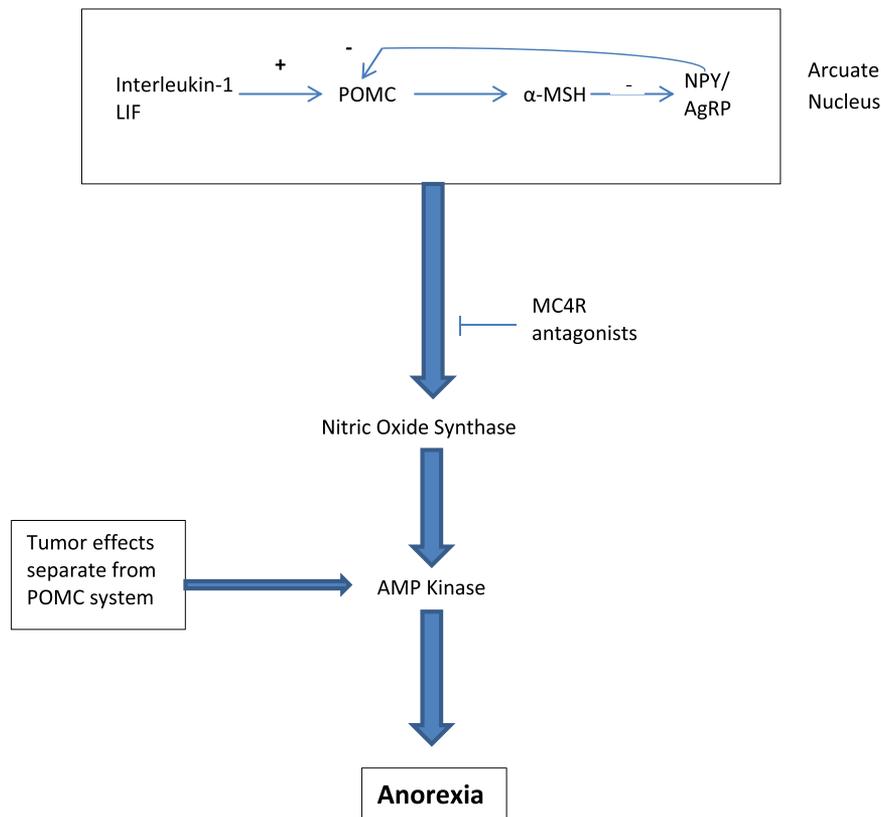
suppression of feeding.<sup>150</sup> Dynamin-1 is responsible for the internalization of EP4 receptors, leading to mitogen-activated protein kinase.<sup>151</sup>

G-proteins play a role in allowing melanocortin coupling to MC4R. Central administration of an antisense to a guanine

nucleotide-binding protein ( $G\alpha_o$ ) subunit slows weight recovery in rats following starvation.<sup>152</sup> In the proteomic profiling,  $G\alpha_o$  was down-regulated two-fold in both anorectic and pair-fed mice.<sup>146</sup> As previously discussed, dopamine plays a role in food intake in tumor-bearing rats. *N*-ethylmaleimide-

**Figure 5** Role of the melanocortin system in tumour-induced anorexia.

POMC = Proopiomelanocortin;  $\alpha$ -MSH = alpha-melanocyte stimulating hormone; MC4R – melanocortin 4 receptor; NPY = neuropeptide Y; AGRP = agouti gene-related peptide; LIF = Leukemia Inhibitory Factor



sensitive factor plays a role in the localization of the  $D_1$  receptor to the membrane.<sup>153</sup> Both  $D_1$  and  $D_2$  receptors were up-regulated in the brains of cancer-bearing rats.<sup>146</sup>

These findings point to proteomic profiling as a useful technique to explore intracellular effects of tumour anorexia. Utilization of mRNA microarrays may prove equally useful. In the C26 colon adenocarcinoma tumour-bearing animals, there were increases in mRNA expression for NPY and AGRP and a decrease for CCK and POMC.<sup>145</sup> Unfortunately, this tumour line, while causing cachexia, actually increased food intake, making these data of little use in understanding cancer anorexia.

## Zinc deficiency

Zinc is a trace element needed in transcription, nutrition, gastrointestinal motility, digestion, oxidative processes, synaptic signalling, signal transduction, memory, ligand binding, apoptosis, and healing.<sup>155–159</sup> Cancer disrupts zinc

metabolism as a result of the acute phase response to inflammatory cytokine activity.<sup>159</sup> There are several mechanisms of zinc deficiency in cancer patients: low albumin reducing zinc binding, anorexia contributing to low intake, ubiquitin–proteasome activation causing accumulation and wasting in muscle cells, gastrointestinal loss, diversion of zinc away from muscle production, and increased urinary excretion of zinc.<sup>160–162</sup> There is limited investigation in the relationship between cachexia and zinc. Normal serum zinc levels are 95.5–99.3  $\mu\text{g}/\text{dL}$ . Lindsey *et al.*<sup>163</sup> identified an average weight loss of 7.6 kg in 10 lung carcinoma patients with a mean zinc level of 71  $\mu\text{g}/\text{dL}$ . These patients also failed to consume about 30% of the recommended dietary allowance of meals daily.

Zinc deficiency is well recognized to produce anorexia.<sup>164</sup> In part, this is because low zinc levels result in hypogeusia.<sup>165</sup> Zinc-deficient animals have a reduced response to norepinephrine-induced and dopamine-induced feeding.<sup>166</sup> Similarly, dynorphin, an endogenous opiate agonist that is a potent orexigenic peptide, has a decreased ability to produce feeding in zinc-deficient animals.<sup>167</sup> Zinc-deficient animals

have lower levels of dynorphin in the hypothalamus. Zinc deficiency in cachexia blocks the release of NPY and administration of zinc results in increased expression of both NPY and orexin mRNA.<sup>168</sup> The putative mechanisms by which zinc deficiency results in cancer anorexia are shown in *Figure 6*.

## Treatment

A number of specific orexigenics have been developed to treat anorexia in cancer patients. They have all been demonstrated to have some utility, but none of them are disease modifying.

### Megestrol acetate

Megestrol was approved by the Food and Drug Administration in the USA to treat anorexia and weight loss in patients with AIDS in 1993. Megestrol is a mixed drug having androgenic, corticosteroid, and progestogenic properties. In rodents, megestrol has been shown to increase NPY in a number of hypothalamic nuclei in both normal and zinc-deficient animals.<sup>169,170</sup> When progesterone increases, NPY activity in the paraventricular nucleus also increases, coinciding with an increase in feeding activity.<sup>171</sup> This suggests that the progestational action of megestrol is a major component in its ability to increase feeding. Corticosteroid Type II receptor stimulation has been also shown to increase NPY gene expression in the hypothalamus.<sup>172</sup> There is also some evidence that megestrol may reduce serotonin.<sup>173</sup> Two studies have also found that megestrol acetate decreases certain cytokines, such as IL-1 and TNF $\alpha$ , most probably secondarily to the corticosteroid effects.<sup>174,175</sup>

Normal doses of megestrol used to enhance appetite are between 600 and 800 mg. A Cochrane meta-analysis found

that megestrol increased weight [risk ratio 1.55 (1.06–2.26), appetite 2.57 (1.48–4.49)] and quality of life (1.02–3.59) in cancer patients. The majority of these studies lasted between 56 and 84 days. Higher doses were more effective for weight gain but had more adverse effects. The adverse effects that were increased included deaths, oedema, dyspnoea, and deep vein thrombosis.<sup>176</sup>

Subsequent to this meta-analysis, megestrol was shown to improve weight gain and reduce anorexia in children with cancer and weight loss.<sup>177</sup> Adrenal suppression was a common side effect in this study. A number of combination studies of megestrol with a variety of other agents ( $\beta$ 2 agonist,<sup>178</sup> meloxicam,<sup>179</sup> celecoxib,<sup>180,181</sup> thalidomide,<sup>182</sup> and olanzapine<sup>183</sup>) have shown improvement in weight gain and appetite, with, in most cases, a better response to the combination agents.

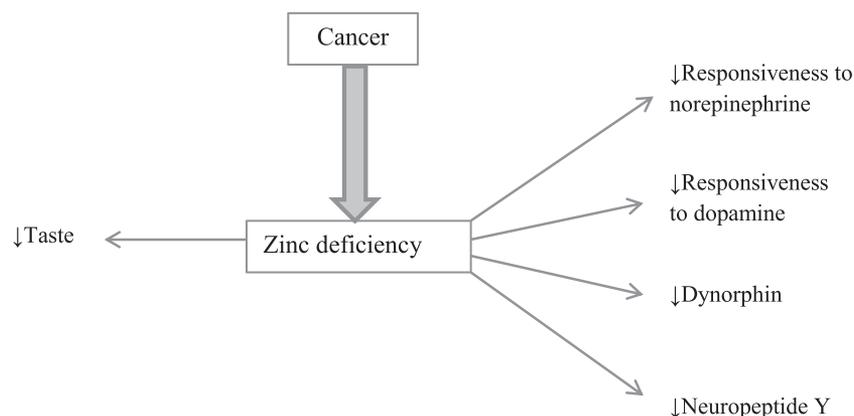
Megestrol acetate has been shown to be poorly absorbed when taken without food.<sup>184</sup> A nanocrystal formulation of megestrol acetate (625 mg/5 mL) has been shown to have greater absorption and bioavailability than megestrol acetate (800 mg/200 mL).<sup>185,186</sup> There is a lack of controlled trials in cancer patients showing an improved clinical outcome with the nanocrystal formulation.

Overall, there is little evidence to support the use of megestrol acetate in cancer patients.

### Cannabinoids

Cannabis has long been recognized to improve appetite (the ‘munchies’), decrease nausea, and enhance food taste.<sup>187</sup> It is now known that endogenous cannabinoids (anandamide) acting through the four-protein coupled-cannabinoid receptors (CB1) increase appetite.<sup>188</sup> Cannabinoids increase NPY in the hypothalamus.<sup>189</sup> Activation of the CB1 receptor results in stimulation of AMP-activated protein kinase.<sup>190</sup>

**Figure 6** Possible mechanisms by which zinc deficiency produces anorexia in cancer.



Another mechanism by which cannabinoids may regulate feeding is directly at the intestinal level where release of anandamide acts as a 'hunger signal' while another fatty acid ethanolamide, oleylethanolamide, is increased during feeding and acts as a satiety signal.<sup>184,191</sup> It appears that these signals are transmitted to the brain through ascending fibres of the vagus nerve. There is some evidence that anandamide may be negatively linked to PYY, which peripherally causes weight loss.<sup>192</sup> When smoked medicinal cannabis was used in HIV-infected adult men, PYY was decreased, and ghrelin levels increased.<sup>193</sup>

In 1994, Nelson *et al.*<sup>194</sup> evaluated the effect of tetrahydrocannabinol on appetite in 18 patients with cancer. Appetite was improved in 13 patients. In patients with AIDS anorexia, dronabinol improved appetite and mood and decreased nausea compared with placebo.<sup>195</sup> There was a tendency for patients on dronabinol to maintain weight better than placebo over the 3 week study period. In the extension of this study, appetite continued to improve, and body weight remained stable.<sup>196</sup> In the study by Jatoi *et al.*<sup>175</sup> on advanced cancer patients, 49% showed an improved appetite, and 3% gained at least 10% of their weight from baseline. Dronabinol in combination with megestrol acetate had no advantages. Strasser *et al.*<sup>197</sup> in a placebo-controlled study of 243 patients

found no significant difference of oral cannabis extract or tetrahydrocannabinol compared with placebo. In an uncontrolled study of malnourished nursing home residents, 53% gained weight.<sup>198</sup> Finally, in patients with advanced cancer, tetrahydrocannabinol enhanced chemosensory perception and appetite.<sup>199</sup> There was also an improved quality of sleep and relaxation.

There is a paucity of evidence to support the use of cannabis in any form to enhance weight gain in cancer patients. On the other hand, the data suggest that it may be an excellent drug for palliative care patients.<sup>200</sup>

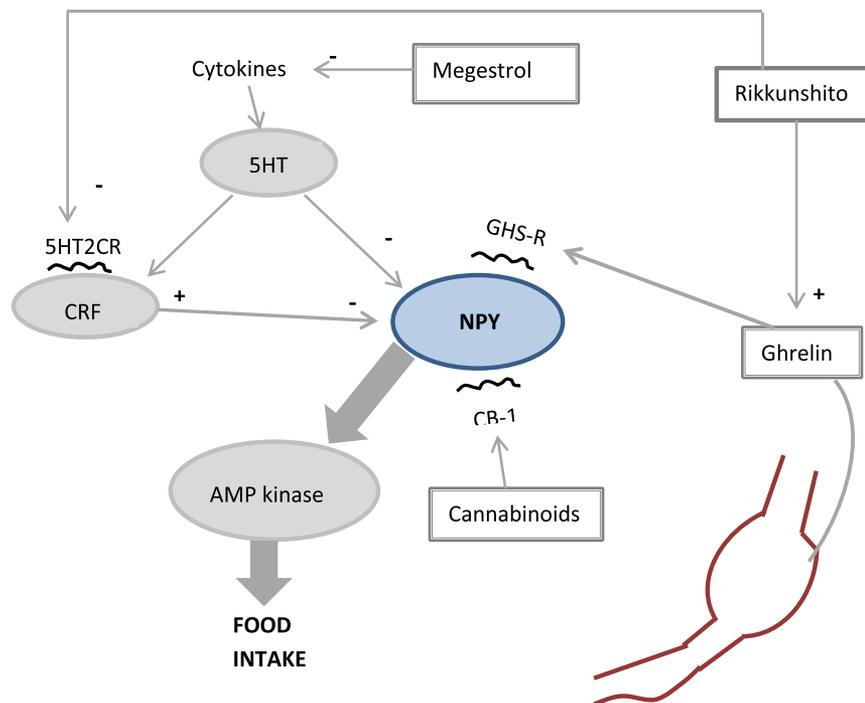
### Ghrelin

Ghrelin is a 28-amino-acid peptide secreted from the fundus of the stomach. It increases food intake through a nitric oxide-dependent mechanism.<sup>121,122</sup> It also improves memory and results in growth hormone release from the pituitary.<sup>201,202</sup>

Patients with cancer cachexia have elevated levels of circulating ghrelin.<sup>106,203,204</sup> In a study of rats implanted with a sarcoma, a long-acting ghrelin analogue (BIM-28131) resulted in increased food intake and weight gain, as well as

**Figure 7** The mechanism(s) by which drugs developed to treat cancer anorexia produce their antral nervous system effects.

SHT = Serotonin; 5HT2cR = Serotonin 2c Receptor; NPY = Neuropeptide Y; CRF = Corticotrophin releasing factor;  
GHS-R = Growth Hormone Secretagogue-Receptor



maintenance of lean mass.<sup>205</sup> The ghrelin analogue's effects were coupled with a significant increase in hypothalamic NPY and AGRP. In another rat tumour-bearing model, ghrelin failed to increase food intake.<sup>206</sup> In this model, NPY was increased, but the increase in AGRP was not different from that in the saline controls. In rats, ghrelin prevented cisplatin-induced anorexia, weight loss, and hyperalgesia.<sup>207</sup> Cisplatin reduces hypothalamic ghrelin secondarily to overactivity of the serotonin 2c receptor<sup>208</sup> and CRF.<sup>209</sup> Animal studies have suggested a Japanese herbal product, Rikkunshito, may enhance peripheral ghrelin secretion and central ghrelin activity through inhibiting the 2HT2c receptor. A recent study suggested that Rikkunshito can suppress cisplatin-induced anorexia in humans.<sup>210</sup> This is in keeping with the low levels of plasma active ghrelin seen during chemotherapy.<sup>211</sup>

A small study in cancer patients with anorexia found that ghrelin could increase food intake and meal appreciation over a single meal.<sup>212</sup> A short-term study in patients with advanced cancer found no effect of ghrelin on nutritional intake nor eating-related symptoms.<sup>213</sup>

Hiura *et al.*<sup>214</sup> studied 42 patients with oesophageal cancer who were receiving cisplatin. They received ghrelin (3 µg/kg) twice daily or saline. Food intake and appetite were improved, and the ghrelin group had less anorexia and nausea following cisplatin. Yamamoto *et al.*<sup>215</sup> found ghrelin reduced weight loss in patients with oesophagectomy and gastric tube reconstruction.

Anamorelin is an oral ghrelin mimetic. In a placebo-controlled crossover study of 16 patients with cancer, anamorelin increased weight gain and appetite.<sup>216</sup> Two studies of anamorelin in non-small-cell lung cancer cachexia are ongoing (ROMANA 1 and ROMANA 2) ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).<sup>217</sup>

Overall, the studies on ghrelin have been somewhat patchy, and there is a need for a substantially powered trial to determine the future of this agent.<sup>218</sup> Figure 7 provides the mechanisms by which drugs used in development of cancer anorexia produce their effects in the central nervous system.

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## Conflict of interest

Chukwuemeka Charles Ezeoke and John E. Morley declare they have no conflicts of interest regarding the writing of this article.

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